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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/187,768	11/06/98	CINCOTTA A	2991/1B206-U

HM12/0814

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EXAMINER	
NICKOL,G	
ART UNIT	**PAPER NUMBER**
1642	15

DATE MAILED: 08/14/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/187,768	CINCOTTA ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-47 and 49-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-47 and 49-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

The request filed on 6-25-01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/187768 is acceptable and a CPA has been established. Claims 34-47 and 49-54 are pending and are currently under consideration. An action on the CPA follows.

All previous rejections and or objections are withdrawn in view of applicant's arguments and amendments there to in Paper No. 12.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 34-36,39, 43 and 49 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3,8, and 13 of U.S. Patent No. 5,792,748 in view of Werning et al. (Arch. Ontolaryngol. Head Neck Surg., July 1995, v121,

pp. 783-789, IDS) and Cincotta et al. (Cancer Research, 1994, Vol. 54, pp. 1249-1258, IDS), as further evidenced by Molitch, ME (Endocrinol.Metab.Clin.North.Am., 1992, Vol. 21(4), Abstract only).

The pending claims are broadly drawn to a method for arresting the growth of or eradicating tumors by adjusting the daily plasma prolactin profile of the tumor bearing mammal by administering a "prolactin enhancer" at appropriate time intervals of day such that the adjusted daily plasma prolactin profile of the tumor bearing mammal conforms to or approaches the normal daily plasma prolactin profile for healthy members for the same species and sex. The claims are further drawn to including in the method *photodynamic therapy* of malignant tumors by "contacting the cells of the tumor with a benzophenoxazine-analog photosensitizer having phototoxicity against tumor cells; and exposing said contacted tumor cells to light, such that the growth of said tumor is retarded or said tumor is eradicated".

US Patent No. 5,792,748 claims the above method, but does **not** include combining photodynamic therapy to eradicate the tumors.

Werning et al. teach that combining PDT with a prolactin enhancer increases the percentage of tumor regression versus PDT alone (abstract). Metoclopramide, as evidenced by Molitch, ME is an prolactin enhancer.

Cincotta et al. teach that 5-ethylamino-9-diethylamino-benzo[a]phenothiazinium chloride (EtNBS), (a benzophenoxazine analog) is a unique photodynamic agent which inactivates solid tumors (page 1257) and that photodynamic therapy of EMT-6 tumors in mice with the 5-ethylamino-9-diethylamino-benzo[a]phenothiazinium chloride resulted in direct tumor cell killing (abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to optimize the claimed invention of Cincatta et al. (US Patent 5,792,748) so as to include photodynamic therapy. One would have been motivated to do so because it was previously taught in the art that the combination of PDT with the administration of a prolactin enhancer resulted in the increased regression of tumors versus PDT therapy alone. Furthermore, the teachings of Cincatta et al. (Cancer Research, 1994) promote the use of highly selective photosensitizers, like EtNBS, for optimizing cell killing in PDT. Thus, clearly, the combined teachings suggest to one of skill in the art a reasonable expectation of success in arresting the growth of or eradicating tumors by combining PDT with the administration of a prolactin enhancer.

Claims 34-36,39, 43 and 49 are directed to an invention not patentably distinct from claims 3,8, and 13 of commonly assigned U.S. Patent No. 5,792,748, for the reasons above.

Commonly assigned U.S. Patent No. 5,792,748, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 CFR 1.78(c) and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g).

Claims 34-35 and 43, 49 are further rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 18 of U.S. Patent No. 6,071,914 in view of Cincotta et al. (Cancer Research, 1994, Vol. 54, pp. 1249-1258, IDS) and Lin, Chi-Wei (Cancer Cells, Vol. 3, No. 11, 1991, IDS).

U.S. Patent No. 6,071,914 claims a method for arresting the growth of or eradicating tumors by adjusting the daily plasma prolactin profile of a tumor bearing mammal, by administering a "prolactin reducer" (i.e. a prolactin inhibitor) and at appropriate time intervals of day such that the adjusted daily plasma prolactin profile of the tumor bearing mammal conforms to or approaches the normal daily plasma prolactin profile for healthy members for the same species and sex.

US Patent No. 6,071,914 does not include combining photodynamic therapy to eradicate the tumors.

Lin summarizes the state of the art of photodyamic therapy (PDT) of malignant tumors including the use of selective photosensitizers like phthalocyanine dyes and iodinated benzophenothiazine (pages 438-439).

Cincotta et al. (Cancer Research) also teach that PDT is a promising new approach for the selective eradication of neoplastic tissue and further teach the successful use of 5-ethylamino-9-diethylamino-benzo[a]phenothiazinium chloride (EtNBS), (a benzophenoxazine analog) as a photosensitizing agent and teach a method of treating tumors in a mammal with EtNBS and that photodynamic therapy of EMT-6 tumors in mice with the 5-ethylamino-9-diethylamino-benzo[a]phenothiazinium chloride resulted in direct tumor cell killing.

In the absence of unexpected results, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine PDT with the patented invention of adjusting prolactin levels with a prolactin inhibitor since each of these methods had been taught by the prior art to successfully eradicate neoplasms. Clearly, the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to produce a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Thus, one of ordinary skill in the art would have reasonably expected to successfully treat tumors using both methods combined.

Claims 34-35, 43 and 49 are directed to an invention not patentably distinct from claim 18 of commonly assigned US Patent No. 6,071,914, for the reasons above.

Commonly assigned U.S. Patent No. 6,071,914, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 CFR 1.78(c) and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 34-47,49-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cincotta et al. (US Patent No. 5,792,748 and/or US Patent 6,071,914) in view of Werning et al. (Arch. Ontolaryngol. Head Neck Surg., July 1995, v121, pp. 783-789, IDS) and Cincotta et al. (Cancer Research, 1994, Vol. 54, pp. 1249-1258, IDS), as further evidenced by Molitch, ME (Endocrinol.Metab.Clin.North.Am., 1992, Vol. 21(4), Abstract only).

The claims are broadly drawn to a method for arresting the growth of or eradicating tumors by adjusting the daily plasma prolactin profile of the tumor bearing mammal by administering a "prolactin enhancer" at appropriate time intervals of day such that the adjusted daily plasma prolactin profile of the tumor bearing mammal conforms to or approaches the normal daily plasma prolactin profile for healthy members for the same species and sex. The claims are further drawn to including in the method *photodynamic therapy* of malignant tumors by "contacting the cells of the tumor with a benzophenoxazine-analog photosensitizer having phototoxicity against tumor cells; and exposing said contacted tumor cells to light, such that the growth of said tumor is retarded or said tumor is eradicated".

1. US Patent 6,071,914 (or 5,792,748) teach a method for inhibiting the growth of neoplasms, in a human mammal having a prolactin profile comprising comparing the prolactin profile of the afflicted mammal to a standard prolactin profile for healthy mammals of the same species and sex and adjusting the prolactin profile of the afflicted mammal to conform to or approach the standard prolactin profile for a mammal of the same species and sex of the afflicted mammal, thereby inhibiting the neoplastic growth (abstract). The patent(s) further teach administering a prolactin enhancer or prolactin reducer wherein said prolactin enhancer includes prolactin as well as substances which increase circulating prolactin levels, i.e. melatonin ('914, column 8, line 4) wherein the latter is administered in an amount within the range of about 0.5 to about 20/mg/person/day ('914, column 8, lines 48-50). The patent(s) further teach administration of the enhancer before or at bedtime which reads on a time between 19:00 and 1:00.

2. Neither US Patent 6,071,914 or 5,792,748 include combining the method with photodynamic therapy of tumors.
3. Werning et al. teach that combining PDT with a prolactin enhancer increases the percentage of tumor regression versus PDT alone (abstract). Metoclopramide, as evidenced by Molitch, ME is an prolactin enhancer.
4. Cincotta et al. teach that 5-ethylamino-9-diethylamino-benzo[a]phenothiazinium chloride (EtNBS), (a benzophenoxazine analog) is a unique photodynamic agent which inactivates solid tumors (page 1257) and that photodynamic therapy of EMT-6 tumors in mice with the 5-ethylamino-9-diethylamino-benzo[a]phenothiazinium chloride resulted in direct tumor cell killing (abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to optimize the claimed invention of Cincatta et al. (US Patent(s) 5,792,748 or 6, 071, 914) so as to include photodynamic therapy. One would have been motivated to do so because it was previously taught in the art that the combination of PDT with the administration of a prolactin enhancer resulted in the increased regression of tumors versus PDT therapy alone. Furthermore, the teachings of Cincatta et al. (Cancer Research, 1994) promote the use of highly selective photosensitizers, like EtNBS, for optimizing cell killing in PDT. Thus, clearly, the combined teachings suggest to one of skill in the art a reasonable expectation of success in arresting the growth of or eradicating tumors by combining PDT with the administration of a prolactin enhancer.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
August 1, 2001

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
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